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(54) Title: COMPLEX OF NAPROXEN AND BETA-CYCLODEXTRIN

(57) Abstract

An inclusion complex of naproxen or a pharmaceutically salt thereof such as naproxen sodium, an unsubstituted or substituted beta-cyclodextrin such as 2-hydroxypropyl-beta-cyclodextrin, and a hydroxylamine such as tromethamine, wherein in the complex, naproxen or the pharmaceutically acceptable salt thereof is included in the beta-cyclodextrin and the hydroxylamine interacts with both naproxen or the pharmaceutically acceptable salt thereof and the beta-cyclodextrin, is useful as a pharmaceutical product.

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COMPLEX OF NAPROXEN AND BETA-CYCLODEXTRIN

BACKGROUND OF THE INVENTION

This invention relates to an inclusion complex of naproxen or a pharmaceutically acceptable salt thereof, a beta-cyclodextrin and a hydroxylamine, and to pharmaceutical compositions containing the inclusion complex.

The solubility and chemical stability of drugs strongly influences successful pharmaceutical formulation. Many drugs from virtually all therapeutic categories suffer from solubility and/or chemical stability problems.

Poorly soluble (hydrophobic) drugs, when orally administered as solid

dosage forms, are slow to dissolve thereby retarding the absorption process which in some cases may lead to incomplete absorption. Slowly dissolving drugs may also exacerbate local side effects produced by the drug (e.g. gastric irritancy). Furthermore it is often difficult, if not impossible, to formulate insoluble drugs for liquid drug delivery via oral, parenteral, ophthalmic, vaginal, nasal or rectal administration without effective drug solubilization. Chemically labile drugs are susceptible to degradation in the solid state, and more frequently in solution, due to hydrolysis, photolysis or oxidation.

Among the variety of techniques available to improve drug solubility (e.g. pH modification, co-solvents, surfactants and the like), cyclodextrins and their derivatives have found extensive application as solubilizers and stabilizers due to their ability to form inclusion complexes with a wide variety of compounds [see (J Szejtli, Cyclodextrin Technology, Kluwer Academic Press) and (J Szejtli & K-H Fromming, Cyclodextrins in Pharmacy, Kluwer Academic Press)].

Cyclodextrins are water soluble cone-shaped cyclic oligosaccharides containing 6, 7 or 8 glucopyranose units. The interior or "cavity" of the cone (hereinafter referred to as the cyclodextrin cavity) is hydrophobic, whilst the exterior is hydrophilic. The size of the cavity increases with increasing number of glucose units. Several cyclodextrin derivatives such as alkyl, hydroxyalkyl and sulfoalkyl ethers have been prepared with improved solubility [see (J Szejtli & K-H Fromming, Cyclodextrins in Pharmacy, Kluwer Academic Press) and (Stella, V J et al, Pharmaceutical Research 1995, 12 (9) S205)]. Suitably sized hydrophobic "guest" molecules may enter the "host" cavity to form a classical host-guest "inclusion compound" or "inclusion complex" with either the entire guest

molecule included or only a portion thereof. The driving mechanism for cyclodextrin inclusion complexation is the affinity of the hydrophobic guest molecule for the cavity of the cyclodextrin host molecule with displacement of cavity water molecules to a thermodynamically more stable state. The term "complex stability" or stability of a given inclusion complex refers to the association/dissociation equilibrium of host and guest in solution. Complex stability depends on the number of intermolecular bonding interactions between the host and guest. Van der Waals forces and hydrophobic interactions are the main interactions stabilizing inclusion complexes (Bergeron. R J et al, Journal of the American Chemical Society 1977,99,5146). Depending on the nature and position of hydrogen bonding functionalities on a given guest, there may be hydrogen bonding between the guest and hydroxyl groups of the cyclodextrin or other hydrogen bonding groups in the case of cyclodextrin derivatives. Ionic interactions between the host and guest are also possible in the case of ionic cyclodextrins such as sulphobutyl ethers (Stella, V J et al Pharmaceutical Research 1995,12(9)S205).

Cyclodextrin inclusion complexes may be prepared on the basis of liquid state, solid state or semi-solid state reaction between the components (J Szejtli, Cyclodextrin Technology, Kluwer Academic Press). The first is accomplished by dissolving the cyclodextrin and guest in a suitable solvent or mixture of solvents and subsequently isolating the solid state complex by crystallization, evaporation, spray drying or freeze drying. In the solid state method, the two components may be screened to uniform particle size and thoroughly mixed whereafter they are ground in a high energy mill with optional heating, screened and homogenized. In the semi-solid state, the two components are kneaded in the presence of small amounts of a suitable solvent, and the complex so-formed, is dried, screened and homogenized.

The liquid state reaction generally provides optimum conditions for completeness of reaction. Depending on solvent conditions, the dissolved inclusion complex exists in equilibrium between uncomplexed host and guest and complexed host/guest.

In many cases, the "fit" of a given drug into a cyclodextrin may allow for only few intermolecular interactions between host and guest leading to a low complex stability with correspondingly limited enhancement of properties such as taste masking, chemical stabilization and solubilization.

In the past in the literature, the term ternary inclusion complex has been used to refer to inclusion complexes which occur when two different guest molecules, neither being water, are incorporated into the same cyclodextrin cavity [see (J Szejtli, Cyclodextrin Technology, Kluwer Academic Press, p 168-169)]. Such ternary complexes are more stable than the corresponding binary complexes due to occupation of greater volume of the cavity in the ternary complex with a greater number of hydrophobic/van der Waals interactions. In cases where organic solvents are used (e.g. ethanol, ether, etc) to prepare inclusion complexes, the solvent may be incorporated into the complex as a ternary component which is difficult to remove.

However, in this application the term ternary complex is used to define a new type of complex, comprising a drug, a cyclodextrin and a third component, wherein the third component interacts with the drug and cyclodextrin from outside the cyclodextrin cavity.

The combination of pH modification together with cyclodextrin complexation has been used to increase the solubility of drugs through the combination of ionization and complexation [see (Loftsson, T et al,

European Journal of Pharmaceutical Science 1993, (1) 95-101), (High solubility multicomponent inclusion complexes consisting of an acidic drug, a cyclodextrin and a base, Chiesi, P et al, PCT Int. Appl., WO 9528965) and (Highly soluble multicomponent inclusion complexes containing a basic drug, an acid, and a cyclodextrin, Chiesi, P et al, PCT Int. Appl., WO 9416733)]. The multicomponent inclusion complexes are prepared by forming an opalescent to clear aqueous solution of the three components, filtering and removal of the water by freeze drying or spray drying. In these cases the combined effect of increasing the solubility of a drug through ionization on the one hand and cyclodextrin complexation on the other hand leads to a greater total solubility of the drug than either ionization or complexation alone. However, ionized guests exhibit up to an order of magnitude lower complex stability than complexes of the corresponding unionized form due to the increased polarity of the ionized form [see (Connors, K A, Journal of Pharmaceutical Sciences 1982,71,217-222), (Orienti, I., et al, European Journal of Pharmacy and Biopharmaceutics 1991,37,110-112) and (Hendrickson, K et al, Australian Journal of Chemistry 1995, 48(6) 1125-1132)]. Thus simple drug ionization with the addition of cyclodextrin leads to an increase in drug solubility, but because the complex stability constant is decreased by ionization, a greater fraction of "free" uncomplexed drug is present which defeats the object of inclusion complexation where chemical stability or taste masking effects (which are dependant on inclusion complexation) are desired.

Large water soluble polymers such as polyvinylpyrrolidone and hydroxypropylmethylcellulose have been used to enhance drug/cyclodextrin complexation and improve drug solubility [see (Loftsson, T, US Pat 5,324,718) and (Loftsson, T et al, International Journal of Pharmaceutics 1995, 126, 73-78)]. Such complexes are prepared by heating aqueous

solutions of the three components and then removal of the water by freeze drying or spray drying if required. The dramatic effect of the polymer and cyclodextrin on increasing the solubility of the drug in a concentration dependant manner was related to an increase in the complex stability of hydrocortisone from solubility isotherm calculation. However in more recent work the same polymers were shown to enhance drug solubility in the absence of cyclodextrin (Loftsson, T et al, International Journal of Pharmaceutics 1996, 127, 193-196). The calculation of complex stability from the initial section of the solubility isotherm (the solubility of guest as a function of cyclodextrin concentration after attaining equilibrium) assumes a 1:1 host/guest stoichiometry and that the increase in guest solubility is proportionally related to host concentration [see (J Szejtli, Cyclodextrin Technology, Kluwer Academic Press, p 143-154)]. If a third component is added to the system which increases guest solubility, the relationship is no longer valid. There is no direct correlation between complex stability and solubility. Other techniques such as potentiometry have been used successfully to determine complex stability constant for different complex species present in solution [see (Connors, K A & Rosanske, T W, Journal of Pharmaceutical Sciences 1980, 69, 173) and (Connors, K A et al, Journal of Pharmaceutical Sciences 1982,71,217-222)].

European Patent Application No 0538011 to Schering Corporation discloses a pharmaceutically acceptable composition of matter comprising a lipophilic oligosaccharide antibiotic, at least about a stoichiometric amount of a base capable of forming a pharmaceutically acceptable salt with the lipophilic oligosaccharide antibiotic such as tromethamine, and an amount of, for example, hydroxypropyl-ß-cyclodextrin sufficient to achieve efficacious delivery of the lipophilic oligosaccharide antibiotic to the serum of an animal, while simultaneously avoiding occurrence of adverse reaction

syndrome, and optionally a pharmaceutically acceptable non-ionic surfactant. It is to be noted that this composition of matter is not a ternary complex of the antibiotic, base and cyclodextrin, but rather an aggregate of the cyclodextrin and the antibiotic in the form of a salt with the base. The antibiotic does not contain any readily ionisable group capable of forming an anion and thus is not readily capable of ionic association with the base.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided an inclusion complex of (a) naproxen or the pharmaceutically acceptable salt thereof, (b) an unsubstituted or substituted beta-cyclodextrin, and (c) a hydroxylamine, wherein in the complex, naproxen or the pharmaceutically acceptable salt thereof is included in the beta-cyclodextrin and the hydroxylamine interacts with both naproxen or the pharmaceutically acceptable salt thereof and the beta-cyclodextrin.

The term "hydroxylamine" includes hydroxyalkylamines.

In the complex, (a) may be naproxen or a pharmaceutically acceptable salt of naproxen, preferably naproxen sodium.

In the complex, (b) may be an unsubstituted beta-cyclodextrin or preferably a substituted beta-cyclodextrin, more preferably 2-hydroxypropyl-ß-cyclodextrin.

In the complex, (c) is a hydroxylamine preferably containing at least one ionisable amino group and one hydroxyl group. The hydroxylamine may

be selected from the group consisting of ammonium hydroxide, tris(hydroxymethyl)aminomethane also known as tromethamine, ethanolamine, diethanolamine, triethanolamine, meglumine also known as N-methylglucamine, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol and 2-amino-1,2,3-propanetriol.

The preferred hydroxylamines are diethanolamine, triethanolamine and tromethamine, most preferably tromethamine.

The inclusion complex preferably has a stoichiometry of (a):(b):(c) mol/mol/mol of 1 : 0,5 to 100 : 1 to 100 ; preferably 1 : 0,5 to 10 : 10 to 100 ; most preferably 1 : 0,5 to 2 : more than 10 to 100.

According to a second aspect of the invention there is provided a pharmaceutical composition comprising as an active ingredient a complex as set out above, and a pharmaceutically acceptable carrier.

The pharmaceutical composition may be formulated for oral, parenteral, ophthalmic, nasal, rectal or vaginal application.

According to a third aspect of the invention there is provided a pharmaceutical composition in the form of a liquid formulation or in the form of a formulation for reconstitution as a liquid formulation, comprising as an active ingredient a complex as set out above, which liquid formulation has a pH of from 5,5 to 8,5 inclusive, preferably from 6,5 to 7,5 inclusive.

The formulation for reconstitution is preferably reconstituted with water at ambient temperature or less.

The formulation may be an effervescent formulation.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the geometry optimised molecular model of a complex formed between naproxen, tris(hydroxymethyl)aminomethane and ß-cyclodextrin;

Figure 2 illustrates the potentiometric titration of an aqueous solution containing naproxen sodium and ß-cyclodextrin as a function of pH using sodium hydroxide as titrant;

Figure 3 illustrates the potentiometric titration of a first aqueous solution containing naproxen sodium, ß-cyclodextrin and tris(hydroxymethyl)aminomethane as a function of pH using sodium hydroxide as titrant; and

Figure 4 illustrates the potentiometric titration of a second aqueous solution containing naproxen sodium, ß-cyclodextrin and tris(hydroxymethyl)aminomethane as a function of pH using sodium hydroxide as titrant.

DESCRIPTION OF EMBODIMENTS

The crux of the invention is a complex formed between (a) naproxen or a pharmaceutically acceptable salt thereof, (b) a ß-cyclodextrin, and (c) a hydroxylamine, wherein the hydroxylamine is capable of simultaneously

interacting with the drug and the cyclodextrin in a manner which increases the drug/cyclodextrin stability under certain conditions of concentration, pH and temperature.

In the complex, there is ionic interaction between a basic group on the hydroxylamine and the acidic group of naproxen, and there is hydrophobic or van der Waals interactions between the included portion of the drug and the cyclodextrin cavity. Optionally there may also be electrostatic, hydrophilic and/or hydrogen bonding interactions between the hydroxy groups of the hydroxylamine and the hydroxy groups and any other complementary substituents on the cyclodextrin.

Brief definitions of the various terms used in the specification are given below

Electrostatic interactions occur between species of opposite formal or partial charge. For example, ionic bonding, is relatively strong (10^2 kcal.mol^{-1}) compared with covalent bonding (10^6 kcal.mol^{-1}) which involves the sharing of electrons between two atoms.

Hydrogen bonding interactions arise when an acidic hydrogen atom (eg OH, NH, SH) on one molecule is attracted towards an electron greedy atom (O,N) on the same or different molecule. Hydrogen bonds are fairly weak interactions (10 kcal.mol^{-1}) and form in preferred directions over distances of less than 2,5Å. A hydrogen bond occurs between polar covalent molecules but is itself electrostatic in nature. Hydrogen bonds may be disrupted by increasing temperature or large deviation of pH from neutrality.

Van der Waals interactions (also known as London dispersion forces) are still weaker forces (1 kcal.mol^{-1}) but are non directional and operate over a distance of less than 4Å. The latter are too weak in themselves to establish a stable molecular species. If, however, a specific spatial arrangement between two molecules allows numerous van der Waals interactions to take place, the species may attain a stability which is comparable with covalent bonding. This is the case with cyclodextrin inclusion complexes where there is a tight fit between host and guest. The presence of electron donating substituents in a guest (eg halogens) enhances van der Waals interactions.

Hydrophilic and hydrophobic interactions are still weaker and involve groups of like polarity or apolarity respectively in relation to the disposition of solvent molecules. Hydrophilic groups will tend to assemble together with associated polar solvent molecules or polar groups, whereas hydrophobic groups will repel polar solvent molecules or groups.

The first component of the complex is naproxen or a pharmaceutically acceptable salt thereof such as for example naproxen sodium. The naproxen is preferably present in the complex as its sodium salt.

The second component of the complex is an unsubstituted or substituted ß-cyclodextrin. For example, the ß-cyclodextrin may be substituted with alkyl, hydroxyalkyl, amino, maltosyl or galactosyl groups. The degree of substitution of the ß-cyclodextrin may vary between 1 and 10 substituents per cyclodextrin molecule.

Preferably, the ß-cyclodextrin used is 2-hydroxypropyl-ß-cyclodextrin having a degree of substitution of from 3 to 7 inclusive.

The third component of the complex is a hydroxylamine.

The hydroxylamine preferably contains at least one ionisable amino group and one hydroxyl group. Suitable hydroxylamines include physiological acceptable water soluble compounds such as ammonium hydroxide, tromethamine, ethanolamine, diethanolamine, triethanolamine, meglumine, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol and 2-amino-1,2,3-propanetriol.

The preferred hydroxylamines are diethanolamine, triethanolamine and tromethamine, most preferably tromethamine.

The complex preferably has a stoichiometry mol/mol/mol of (a):(b):(c) of from 1 : 0,5 to 100 : 1 to 100 ; more preferably 1 : 0,5 to 10 : 10 to 100 ; most preferably 1 : 0,5 to 2 : more than 10 to 100.

It has to be noted that the use of higher levels of the hydroxylamine increases the taste masking effects of the complex and thus leads to a complex which gives a more palatable pharmaceutical formulation. Taste masking is one of the particular advantages of the complex of the invention as will be detailed below.

The complex of the invention may be prepared according to any one of the following general methodologies:

1 The hydroxylamine and the drug are blended to form a solution or slurry with optional use of water. The mixture is added to a concentrated solution of the cyclodextrin which may be optionally buffered to around neutral pH with a pharmaceutically

acceptable buffer such as phosphate buffer. The solution may be heated to effect dissolution. The system is agitated for 0.5 to several hours until equilibrium is reached to obtain the liquid complex.

2 The solution obtained in Step 1 may be precipitated, spray dried or freeze dried to obtain the solid complex.

3 The hydroxylamine and the drug are blended to form a paste with optional use of water. The cyclodextrin is added portion-wise to the paste with vigorous mixing and occasional addition of water to maintain the paste consistency. The mixture is kneaded for 0.5 to several hours. The paste may be extruded and dried in the form of pellets or directly dried in vacuo with heating and screened to uniform particle size.

4 The hydroxylamine and the cyclodextrin are blended to form a paste with use of water. The drug is added portion-wise to the paste with vigorous mixing and occasional addition of water to maintain the paste consistency. The mixture is kneaded for 0.5 to several hours. The paste may be extruded and dried in the form of pellets or directly dried in vacuo with heating and screened to uniform particle size.

The liquid complex obtained in step 1 may be adapted for parenteral, ophthalmic, topical, oral, vaginal or rectal application by addition of pharmaceutically acceptable excipients such as anti-oxidants (eg EDTA, N-acetylcysteine), co-solvents (eg polyethyleneglycol, propyleneglycol), viscosity modifiers (eg hydroxypropylmethylcellulose), osmolality modifying

agents (eg sorbitol, mannitol), pH modifying agents (eg HCl, NaOH, phosphate buffers), sweeteners (eg sodium cyclamate, sodium saccharin, sucrose) or flavours.

The complexes obtained in steps 2, 3 or 4 may be adapted for use in the conventional formulation of tablets, capsules, suppositories, pessaries, nasal and pulmonary inhalations and topical applications.

The pharmaceutical composition of the invention is preferably in the form of a liquid formulation or in the form of a formulation for reconstitution as a liquid formulation, which liquid formulation has a pH of from 5,5 to 8,5 inclusive, or preferably from 6,5 to 7,5 inclusive.

The advantages of the complex of the invention will now be discussed.

It is known that naproxen forms stable inclusion complexes with beta-cyclodextrins, and to a lesser extent, with alpha and gamma-cyclodextrins. Complexation of naproxen or its sodium salt with beta-cyclodextrins does not however lead to effective taste masking of naproxen, presumably due to the relatively low association constant of the naproxen/beta-cyclodextrin complex ($K_{ASS} < 500M^{-1}$) at neutral or physiological pH which leads to rapid dissociation of the complex in the oral cavity. The ternary complex formed between naproxen sodium/tromethamine/hydroxypropyl-beta-cyclodextrin, for example, has a bland taste when dissolved in water compared with a strong burning sensation produced by a similar binary naproxen sodium/hydroxypropyl-beta-cyclodextrin complex at equivalent pH. The rationale underlying the effect of taste masking of the ternary complex is a significantly increased association constant due to a combination of ionic, hydrogen bonding and van der Waals interactions as

opposed to exclusive van der Waals interactions in the binary system. The increased association constant of the ternary complex retards dissociation of naproxen in the oral cavity and thereby masks its taste.

Thus, the first important advantage of the complex of the invention is taste-masking.

Other advantages of the complex are:

increase in water solubility of the drug;
increased stabilisation of the drug molecule to chemical or photodegradation;
decreased irritant effects, for example gastric irritation, burning of parenteral or ophthalmic solutions, rectal or vaginal intolerance; and
improved rate and extent of drug absorbtion.

Figure 1 shows the geometry optimised molecular model of the complex formed between naproxen, tris(hydroxymethyl)aminomethane and ß-cyclodextrin.

Figure 2 shows the potentiometric titration of an aqueous solution containing naproxen sodium (3 mmol) and ß-cyclodextrin (15 mmol) as a function of pH using sodium hydroxide as titrant. The temperature and ionic strengths were controlled to 25°C (±0,2°C). The 5 fold excess in cyclodextrin concentration was chosen to maximize complexation of naproxen. The percentage of naproxen (NP) species was determined as the anion NP^-, protonated acid (NPH), the 1:1 ß-cyclodextrin inclusion complex [(CD)(NPH)] and the corresponding 2:1 complex $[(CD)_2(NPH)]$ by potentiometry and equilibrium simulation for titration analysis computation.

Titrations were carried out under a stream of dinitrogen in order to exclude atmospheric carbon dioxide. A computer was used to control the addition of titrant from a Radiometer ABU80 burette. After each incremental addition of titrant, the computer recorded the emf measured by a Radiometer research pH meter between Metrohm electrodes immersed in the titrant solution. The results clearly indicate that naproxen does not participate in inclusion complexation with ß-cyclodextrin to any significant extent at pH values above 6,5 at which naproxen exists exclusively as the free anion (NP^-). Below pH 6,5 the protonated acid (NPH), the 1:1 ß-cyclodextrin inclusion complex [(CD)(NPH)] and the corresponding 2:1 complex [$(CD)_2$ (NPH)] are detected in varying proportions.

Figure 3 shows the potentiometric titration of an aqueous solution containing naproxen sodium (3 mmol), ß-cyclodextrin (15 mmol) and tris(hydroxymethyl)aminomethane (TR)(3 mmol) as a function of pH using sodium hydroxide as titrant. Experimental conditions were as described above for Figure 2. Under these conditions it was found that an equimolar proportion of TR relative to NP produced complexes according to the invention as follows:

pH 2,3 - 6,5 $(CD)(TR)(NP^-)H^+)_2$ with maximum concentration of 50% occurring around pH 3,3;

pH 3,0 - pH 9,8 $(CD)(TR)(NP^-)(H^+)$ with maximum concentration of 30% occurring around pH 7,0.

Figure 4 shows the potentiometric titration of an aqueous solution containing naproxen sodium (0,00872 mmol), ß-cyclodextrin (0,00908 mmol) and tris(hydroxymethyl)aminomethane(TR)(0,0908 mmol) as a function of pH using a sodium hydroxide as titrant. Experimental conditions were as described above for Figure 2. Under these conditions it was found that a

ten fold molar excess of TR relative to equimolar NP and CD produced complexes according to the invention as follows:

pH 2,3 - 7,2 $(CD)(TR)(NP^-)(H^+)_2$ with maximum concentration of 85% occurring around pH 3,3;

pH 3,0 - pH 9,8 $(CD)(TR)(NP^-)(H^+)$ with maximum concentration of 60% occurring around pH 7,0.

Referring to Figure 1 there is shown the geometry optimised molecular model of the complex formed between naproxen, tris(hydroxymethyl) aminomethane and ß-cyclodextrin. The species can be identified in solution by means of potentiometric titration at 25°C using sodium hydroxide as titrant. In the absence of the ligand, no complexation is observed between ionised naproxen and ß-cyclodextrin above pH 7 (see Figure 2). In the presence of increasing concentrations of the ligand, the complex proportionally forms preferentially around neutral pH (see Figures 3 and 4) indicating dramatic increase in naproxen-cyclodextrin complex stability at neutral and higher pH. This surprising finding indicates involvement of considerable intermolecular forces exerted by the ligand in stabilising the complex as seen in the molecular mechanics of the system shown in Figure 1.

It is important to note that from the experiment represented in Figure 4, complexation at neutral pH was doubled using ten times the amount of tris(hydroxymethyl)aminomethane and decreasing the amount of cyclodextrin three times, relative to the experiment represented by Figure 3. This is surprising since one would expect decreased complexation when reducing the concentration of cyclodextrin. This unexpected observation clearly shows the concentration dependant effect of tris(hydroxymethyl)aminomethane in enhancing complexation of ionised

naproxen.

It is further important to note that tris(hydroxymethyl)aminomethane promotes complex formation near pH 7. A comparison of Figures 2 and 3 shows that, in the absence of tris(hydroxymethyl)aminomethane, no significant ß-cyclodextrin/naproxen complexation is detectable at pH 7.

Various examples of the invention will now be given.

Example 1

2-hydroxypropyl-beta-cyclodextrin (140g) and tromethamine (13.15 g) are triturated with a small quantity of purified distilled water to form a viscous paste. Naproxen (25g) is gradually added with vigorous mixing for 1 hour. The paste is dried under vacuum (2mbar) at 40°C. The dried complex (1:1:1) is sieved through a 710 micron sieve.

Example 2

A unit dose of a granular formulation suitable for reconstitution in water is as follows:

Complex of Example 1 (eq. to 200mg naproxen)	1,429g
Saccharin	0,030g
Mint flavour (spray dried)	0,120g

Excipients are mixed with the complex, screened through a 60 mesh screen and packed into sachets.

The contents of the sachet are added to 100ml tap water to provide a clear, pleasant tasting solution.

Example 3

2-Hydroxypropyl-beta-cyclodextrin (140g) and tris(hydroxymethyl)aminomethane (120.0 g) are triturated with a small quantity of purified distilled water to form a viscous paste. Naproxen sodium (25 g) is gradually added with vigorous mixing for 1 hour. The paste is dried under vacuum (2mbar) at 40°C The dried complex (1 : 10 : 1 naproxen sodium : tromethamine : cyclodextrin) is sieved through a 710 micron sieve.

The complex formed is void of the bitter, burning taste sensation produced by naproxen. Solutions of naproxen-cyclodextrin complexes produced in the absence of the hydroxylamine produce a severe burning sensation and bitter taste.

Example 4

The complex prepared according to Example 3 may be incorporated in a unit dose of a granular formulation suitable for reconstitution in water at room temperature as follows:

Complex of Example 3 (equivalent to 200mg naproxen)	2.706g
Saccharin	0.030g
Mint flavour (spray dried)	0.120g

Excipients are mixed with the complex, screened through a 60 mesh screen and packed into sachets. On reconstitution with tap water the product is palatable and free from the bitter and burning taste sensation produced by naproxen.

Example 5

Complex of Example 3 (equivalent to 200mg naproxen)	2.706g
Saccharin	0,030g

Mint flavour (spray dried)	0.100g
Sodium carbonate	0.600g
Tartaric acid	1.000g
Magnesium stearate	0.375g

Excipients excluding tartaric acid and lubricant are mixed with the complex, and screened through a 60 mesh screen. The mixture is optionally granulated with the use of a water soluble binder such as polyvinylpyrollidone. The granulate is blended with the tartaric acid. The lubricant is screened into the mixture and blended. The product is compressed into effervescent tablets.

The product reconstituted in water at room temperature is pleasant tasting and free from the bitter and burning taste sensation produced by naproxen.

CLAIMS

1 An inclusion complex of (a) naproxen or a pharmaceutically acceptable salt thereof, (b) an unsubstituted or substituted beta-cyclodextrin, and (c) a hydroxylamine, wherein in the complex, naproxen or the pharmaceutically salt thereof is included in the beta-cyclodextrin and the hydroxylamine interacts with both naproxen or the pharmaceutically acceptable salt thereof and the beta-cyclodextrin.

2 An inclusion complex according to claim 1 wherein (a) is naproxen sodium.

3 An inclusion complex according to claim 1 or claim 2 wherein (b) is 2-hydroxypropyl-beta-cyclodextrin.

4 An inclusion complex according to any one of claims 1 to 3 wherein (c) is selected from the group consisting of ammonium hydroxide, tris(hydroxymethyl)aminomethane, ethanolamine, diethanolamine, triethanolamine, meglumine, 2-amino-2-methyl-1,3-propanediol, 2-amino-2-methyl-propanol and 2-amino-1,2,3-propanetriol.

5 An inclusion complex according to claim 4 wherein (c) is selected from the group consisting of diethanolamine, triethanolamine and tromethamine.

6 An inclusion complex according to claim 5 wherein (c) is tromethamine.

7 An inclusion complex according to any one of claims 1 to 6 wherein

the inclusion complex has a stoichiometry of (a):(b):(c) mol/mol/mol of 1:0,5 to 100: 1 to 100.

8 An inclusion complex according to claim 7 wherein the inclusion complex has a stoichiometry of (a):(b):(c) mol/mol/mol of 1 : 0,5 to 10 : 10 to 100.

9 An inclusion complex according to claim 8 wherein the inclusion complex has a stoichiometry of (a):(b):(c) mol/mol/mol of 1 : 0,5 to 2 : more than 10 to 100.

10 An inclusion complex of (a) naproxen sodium, (b) 2-hydroxypropyl-beta-cyclodextrin, and (c) tromethamine, wherein in the complex, naproxen sodium is included in 2-hydroxypropyl-beta-cyclodextrin and tromethamine interacts with both naproxen sodium and 2-hydroxypropyl-beta-cyclodextrin, the complex having a stoichiometry of (a):(b):(c) mol/mol/mol of 1:0,5 to 100: 10 to 100.

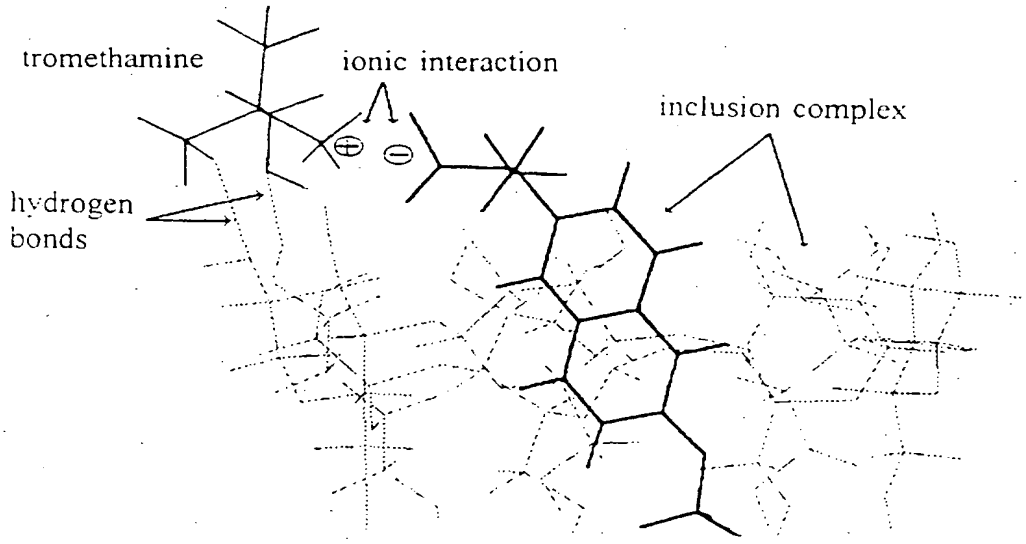
11 A pharmaceutical composition comprising as an active ingredient an inclusion complex according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

12 A pharmaceutical composition in the form of a liquid formulation or in the form of a formulation for reconstitution as a liquid formulation, comprising as an active ingredient an inclusion complex according to any one of claims 1 to 10, which liquid formulation has a pH of from 5,5 to 8,5 inclusive.

13 A pharmaceutical composition according to claim 12 wherein the

liquid formulation has a pH of from 6.5 to 7.5 inclusive.

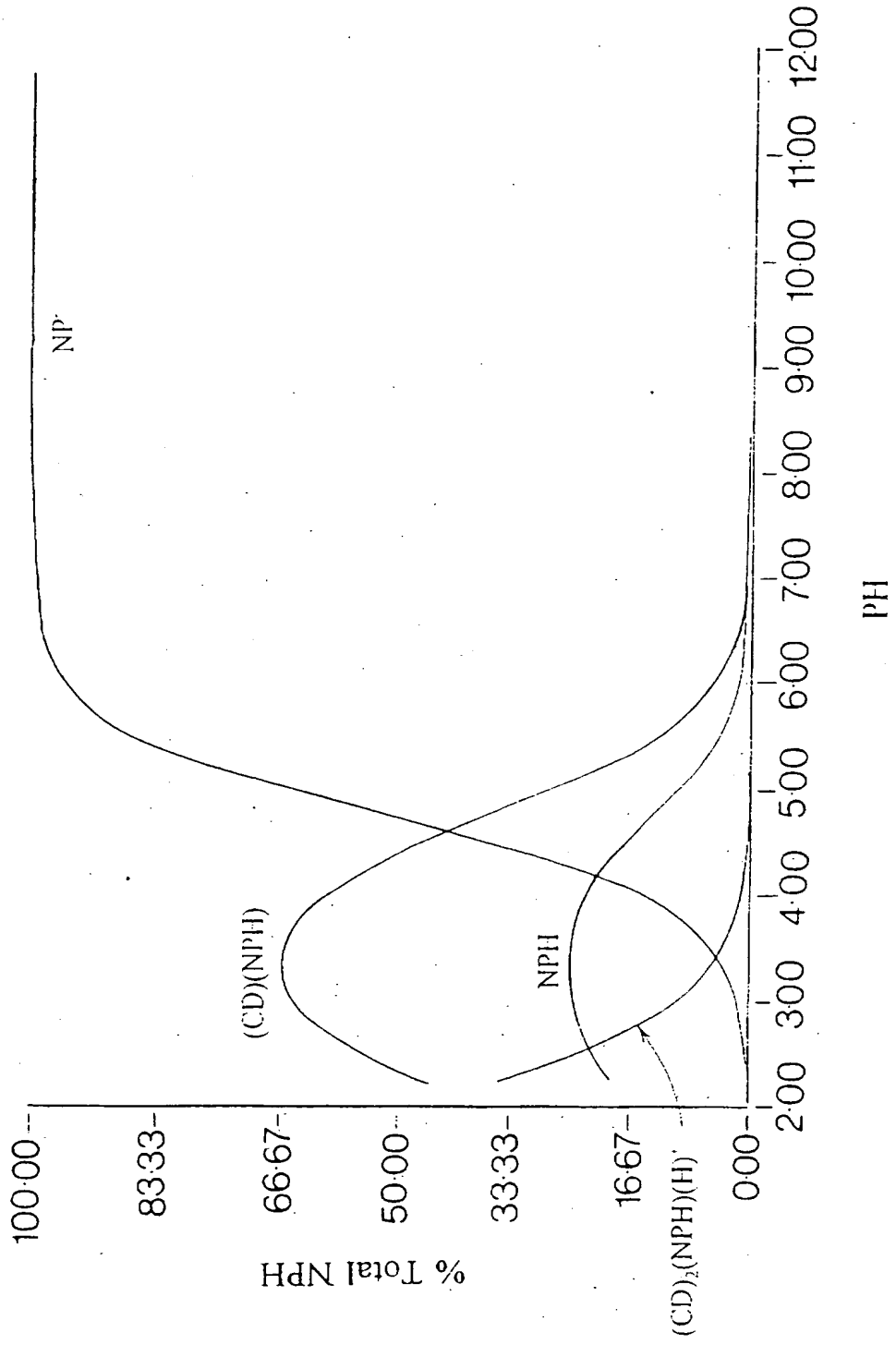
14 A pharmaceutical composition according to claim 12 or claim 13 wherein the formulation for reconstitution is reconstituted with water at ambient temperature or less.



naproxen (bold) - beta-cyclodextrin complex

Fig 1

Fig 2


NP
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NPH
(CD)2(NPH)(H)
% Total NPH
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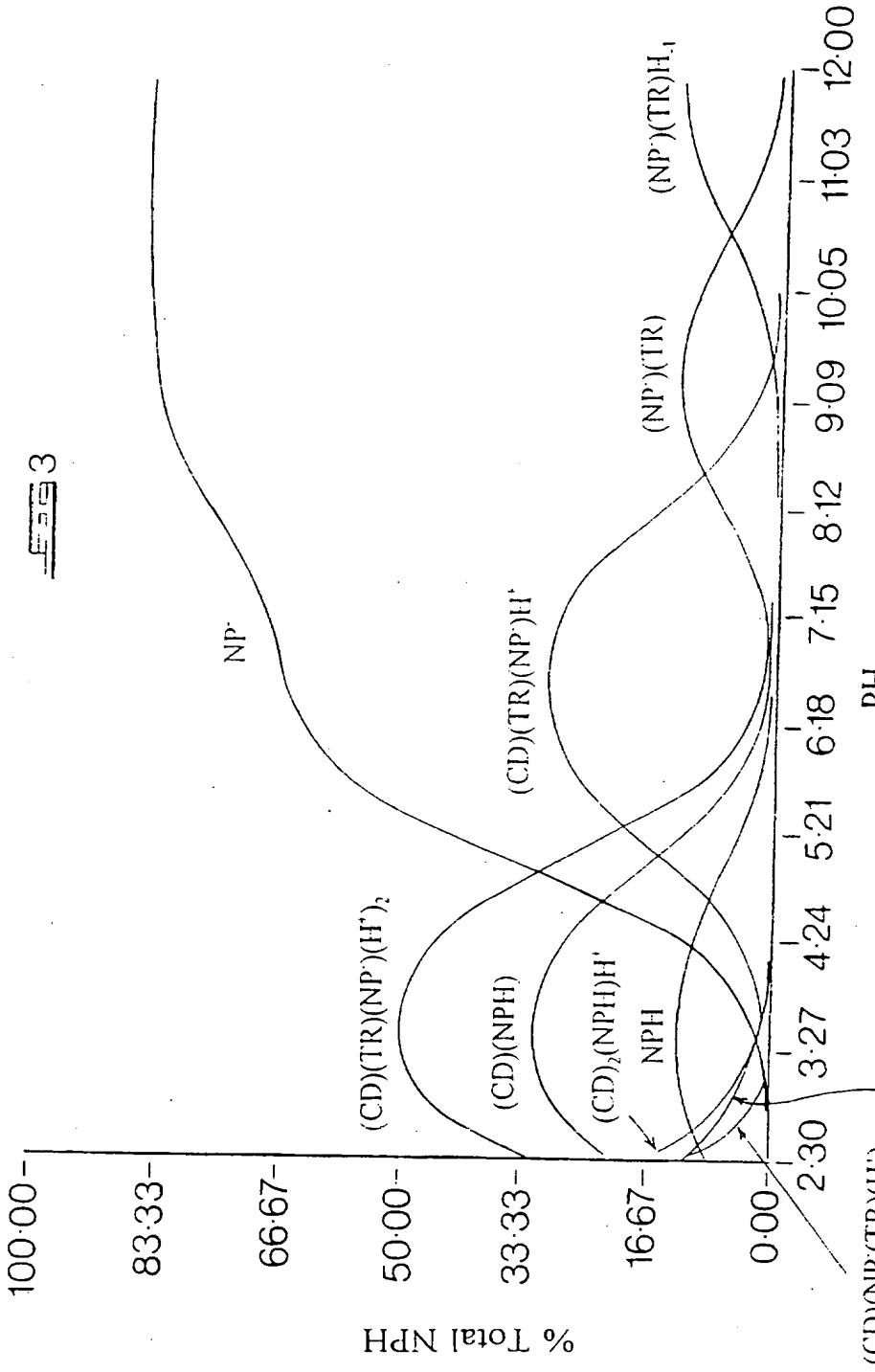
83·33
66·67
50·00
33·33
16·67
0·00
2·00
3·00
4·00
5·00
6·00
7·00
8·00
9·00
10·00
11·00
12·00
PH


% Total NPH
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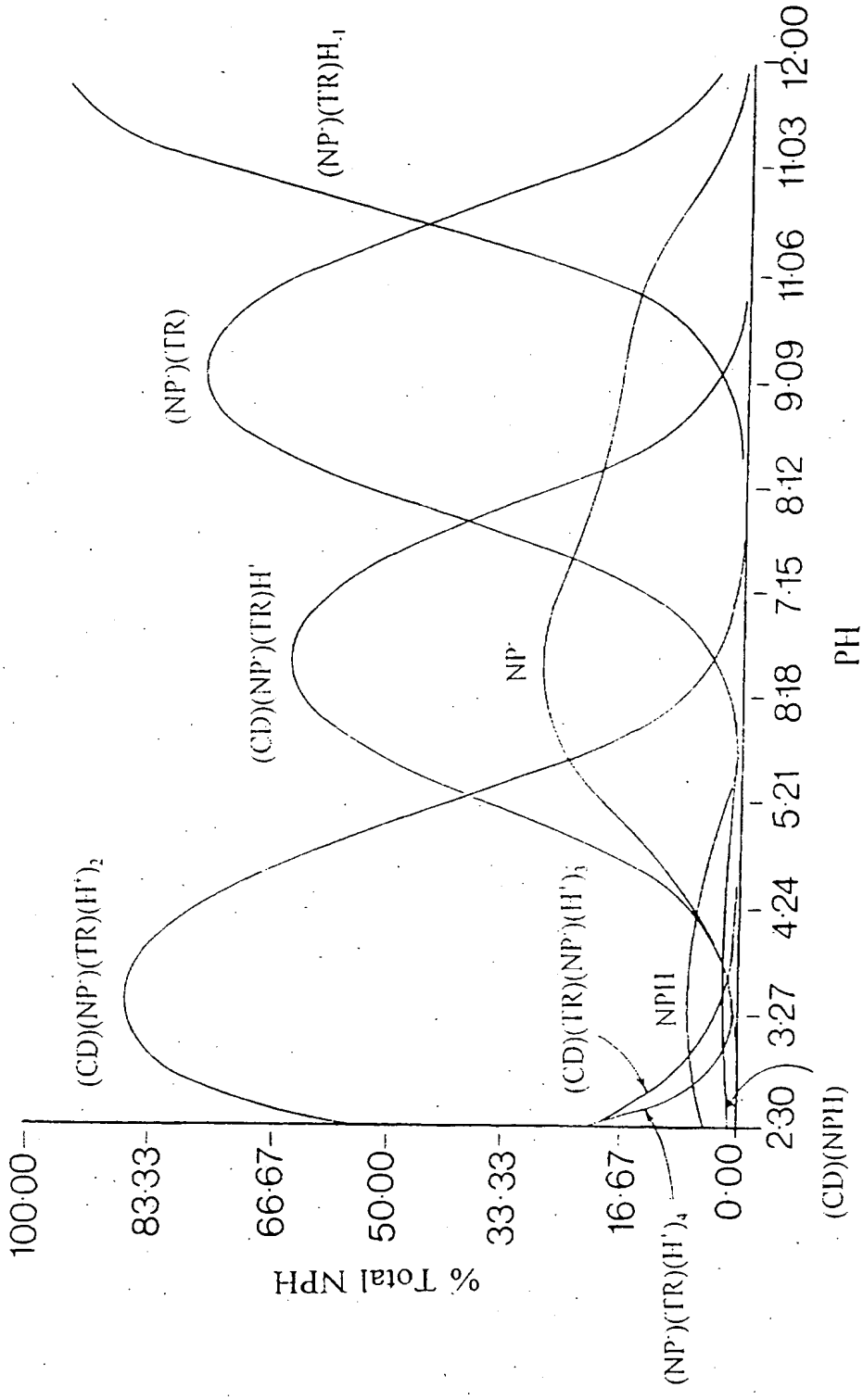
83·33
66·67
50·00
33·33
16·67
0·00
2·30
3·27
4·24
5·21
6·18
7·15
8·12
9·09
10·05
11·03
12·00
PH
NP'
(CD)(TR)(NP')(H')2
(CD)(NPH)
(CD)2(NPH)H'
NPH
(CD)(TR)(NP')H'
(NP')(TR)
(NP')(TR)H-1
(CD)(NP')(TR)(H')3
(CD)(NP')(TR)(H')4

Fig 3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7:15
8:12
9:09
11:06
11:03
12:00
PH
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(NP')(TR)H'1
(NP')(TR)
(CD)(NP')(TR)H'
NP'
(CD)(TR)(NP')(H')2
NPH
(NP')(TR)(H')3
(CD)(NP')(TR)(H')2

Fig 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 96/01367

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C08B37/16 A61K31/715 A61K47/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C08B A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 95 28965 A (CHIESI FARMACEUTICI S.P.A.) 2 November 1995 cited in the application see page 5, line 19 - line 31 ---	1-14
Y	EP 0 273 890 A (ASTRA LAKEMEDEL AKTIEBOLAG) 6 July 1988 see page 3, line 56 see page 4, line 9 - line 13 ---	1-14
Y	WO 95 07104 A (SMITHKLINE BEECHAM PLC) 16 March 1995 see page 4, line 4 - line 25 see examples 7-9A ---	1-14
A	US 4 994 260 A (KÄLLSTRAND ET AL.) 19 February 1991 --- -/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 February 1997	12. 03. 97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Lensen, H

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INTERNATIONAL SEARCH REPORT

Inter[redacted] Application No
PC[redacted]/IB 96/01367

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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